

Applicants: Andrzej Lipkowski et al.
Serial No.: 10/524,343(a §371 of PCT/PL2003/000077)
Filed : January 30, 2006
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REMARKS

Claims 2-3 and 5-9 are pending in the subject application with claims 11-16 and 18-23 withdrawn from consideration.

Claims Rejected Under 35 U.S.C. §103(a)

Claims 2,3 and 6-8

The Examiner rejected claims 2, 3 and 6-8 under 35 U.S.C. §103(a) as allegedly obvious over Ronai et al. (*Biochem. Biophys. Res. Comm.*, 1979, 91:1239-1249) in view of Abbruscato et al. (*J. Neurochem.*, 1997, 69:1236-1245) and Kanai et al. (*J. Biol. Chem.*, 1998, 273:23629-23632). The Examiner asserted that it would have been obvious to one of skill in the art, in light of Kanai et al., to, inter alia, (1) "substitute Met for Ala, to see what effect it would have on the analog potency and transport system" and (2) "modify the C-terminus of the peptide" and (3) "make a dimeric peptide analog of enkephalin." In addition, in the June 6, 2008 Advisory Action the Examiner indicated, with regard to replacing an amino acid of the dimer compounds discussed in Abbruscato et al., that Kanai et al. teach that "methionine worked as well as the other amino acids (except for Phe and Trp)".

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In response, applicants respectfully traverse the Examiner's rejection.

Unexpected results

Applicants note that the claimed compounds, unlike prior opiate compounds, do not cause respiratory depression when administered at high doses (see page 4, line 28 to page 5, line 3). This characteristic of the claimed compound (which is an undesirable effect of prior art compounds, see page 2, lines 20-22) is of great importance in their expected uses, and, significantly was not expected (see page 5, lines 28 and 29).

Accordingly, applicants maintain that the compound as claimed possesses an unexpected property, and that the compound is not obvious over the cited combination of prior art.

Unpredictability

The *cumulative effect* of modifications to the prior art proposed by the Examiner to somehow arrive at the claimed invention have unpredictable effects, and were known to be unpredictable by those skilled in the art at the time. The Examiner's reasoning requires three modifications to somehow arrive at the claimed invention. Applicants have previously noted the unpredictability associated with each of these modifications. The Examiner has taken a position in response to this argument of applicants, but has still not addressed the *cumulative effect* of these modifications on predictability of the claimed invention.

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Applicants maintain that the invention as claimed was not predictable in light of the cumulative effect of the predictability issues associated with the modifications.

Selection from Prior Art Made By Examiner

Applicants note that the Examiner has suggested that in view of Kanai et al. it would be obvious to one of ordinary skill in the art to substitute one of the amino acids in the dimer of Abbruscato et al. However, the Examiner has selected, out of multiple options, the substitution of an alanine with a methionine when (a) there are multiple amino acids besides methionine disclosed in Kanai et al. and (b) two of those recited in Kanai et al., as the Examiner acknowledges, are superior to methionine for the role that the Examiner has indicated is the reason for their substitution. The Examiner states that "methionine worked as well as the other amino acids (except for Phe and Trp)". Thus, the Examiner is arguing that the substitution with an *inferior* choice of amino acid is obvious. Applicants respectfully disagree and maintain that an obvious rejection based in part on this is improper, and should be withdrawn. Kanai et al. clearly does not teach the selection of methionine.

Applicants respectfully maintain that, for the reasons set forth hereinabove, the invention as claimed is not obvious and respectfully request reconsideration and withdrawal of this ground of rejection.

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Claims 2, 3 and 5-9

The Examiner rejected claims 2, 3 and 5-9 under 35 U.S.C. §103(a) as allegedly obvious over Ronai et al. (*Biochem. Biophys. Res. Comm.*, 1979, 91:1239-1249) in view of Abbruscato et al. (*J. Neurochem.*, 1997, 69:1236-1245) and Kanai et al. (*J. Biol. Chem.*, 1998, 273:23629-23632) in further view of Hill et al. (U.S. Patent No. 5,880,132), Bock et al. (EP 0434369) and Ornstein (U.S. Patent No. 5,356,902). The Examiner asserted that Ornstein, Hill and Bock et al. teach stimulatory amino acids, tachykinins and cholecystokinin receptor antagonists, and that Abbruscato et al. teaches biphalin, and that it would have been obvious to one of skill in the art to combine the teachings of the cited art to arrive at the invention as claimed.

In response, applicants respectfully traverse the Examiner's rejection. Applicants have stated hereinabove why the invention as claimed is not obvious over the combination of Ronai et al., Abbruscato et al., and Kanai et al. Applicants further note that the teachings of Hill et al., Bock et al. and Ornstein, in combination with the remaining cited art, do not cure these deficiencies. The combination of references does not teach or suggest a compound with the unexpected properties of (Tyr-D-Met-Gly-Phe-NH-)₂, and does not teach or suggest applicants' invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.